tachycardia, sinus pauses > 2 s, QRS enlargement > 0.12 s, hypotension) didn't differ among patients aged ≤ 60 or > 60 years, either in pts treated with PFN (16% and 14% respectively) or PLA (8% and 8% respectively). In conclusion, the high efficacy of PFN as single oral loading dose in recent-onset AF without signs of heart failure is confirmed even in elderly subjects, with a favourable safety profile. Moreover, conversion to SR after PLA appears to occurr less frequently in elderly patients.

1052 Pharmacologic Modulation of Vascular-Endothelial Function

Wednesday, March 19, 1997, 9:00 a.m.–11:00 a.m.
Anaheim Convention Center, Hall E
Presentation Hour: 9:00 a.m.–10:00 a.m.

1052-132 Acute Hemodynamic and Renal Effects of the Endothelin-1 Receptor Antagonist TAK-044 in Patients Without Heart Failure

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Endothelin-1 participates in the regulation of arteriolar and venous tone in patients (pts) with markedly impaired left ventricular (LV) function and congestive heart failure (CHF). However, its role in the regulation of vascular tone in the absence of CHF in not established. Accordingly, we tested the acute effects of single dose, randomized administration of TAK-044 (25, 50 or 100 mg), an endothelin-1 type A and B receptor antagonist, or matching placebo given over 15 minutes intravenously on cardiac and renal hemodynamics in 24 pts (56 ± 6 years, 5 females, 19 males) with LV ejection fraction ≥ 40% and no CHF. Regular medication was discontinued the day before the study. Renal (para-aminohippuric acid and inulin clearance) and cardiac hemodynamics (pulmonary and radial artery catheters, and ECG, respectively) were determined before and during 4 hours after infusion. Because there was no clear dose-response relationship, all TAK-044 pts (n = 17) were treated as a group and compared to placebo (n = 7). TAK-044 reduced mean arterial (7.8 mmHg), pulmonary (4 mmHg) as well as pulmonary capillary wedged pressures (1.5 mmHg [differences of all measurements vs. placebo; $p < 0.01$]). Cardiac index increased (0.25 mL/min/BSA) and heart rate and right atrial pressure were unchanged. Systemic vascular resistance fell (114 dynes.sec.cm^{-5}). Renal plasma flow increased non-significantly and glomerular filtration rate was unchanged by TAK-044. Accordingly, renal vascular resistance fell (mean 14.1%, $p < 0.05$) and this change was similar to that of systemic vascular resistance (mean 22.8%, $p < 0.01$). Thus, in pts with no symptoms of CHF, endothelin-1 also contributes to arteriolar tone and systemic receptor blockade leads to vasodilation and improves cardiac index. The lack of influence on right atrial pressure suggests no major effects on venous tone. Finally, the renal circulation in these pts is not particularly sensitive to the effects of blockade.

1052-133 N-acetylcysteine Improves Coronary Vascular Endothelial Dysfunction

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Reduced endothelial nitric oxide (NO) availability in patients (pts) with atherosclerosis may be due to increased breakdown of NO by oxygen free radicals. Reduced thiols such as N-acetylcysteine (NAC) may improve the bioavailability of NO by their antioxidant effects or by forming stable adducts of NO. To investigate whether coronary vascular endothelial dysfunction can be improved by NAC, we studied the effect of intracoronary NAC (48 mg/min) on the responses to acetylcholine (ACh, 30 μg/min), sodium nitroprusside (SNP), and adenosine in 17 pts with normal coronary arteries or mild atherosclerosis of epicardial coronary arteries. Diameter (D mm) was measured by quantitative angiography, and coronary vascular resistance (R) was estimated using Doppler flow velocity.

	ACh		SNP		Adenosine	
	%↓R	D	%↓R	D	%↓R	D
Control	−33	1.9	−8	2.4	−75	2.5
NAC	−48	2.1	−42	2.5	−74	2.5
P Value	0.003	0.002	0.006	0.001	0.8	0.8

Intracoronary NAC infusion had no effect on resting hemodynamics, but improved microvascular and epicardial vasodilation in response to ACh and SNP, but not to adenosine. The effect of NAC was more pronounced in pts with depressed response to ACh. Thus, NAC specifically enhances the effects of endogenous (stimulated by ACh) and exogenous NO (SNP) on the coronary vasculature and may have potential therapeutic value in pts with endothelial dysfunction.

1052-134 Vasodilator Effects of Brain Natriuretic Peptide in Coronary Conductance and Resistance Arteries

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Brain natriuretic peptide (BNP) is a hormone secreted predominantly by ventricular myocytes in heart failure, presumably as a compensatory vasodilatory mechanism. It has been shown to ameliorate symptoms and EKG abnormalities in patients with coronary spasm. BNP-induced vasodilation in vitro is mediated via increased cGMP. We examined the coronary vasodilatory effects of BNP in vivo in 20 anesthetized pigs. Epicardial coronary cross-sectional area (CSA) was measured by intracoronary ultrasound; average coronary peak flow velocity (APV) was simultaneously measured by Doppler velocimetry; and volumetric coronary blood flow (CBF) was calculated. In 14 pigs, intracoronary BNP (1 pM to 0.1 μM) induced significant dose-dependent increases in CSA (12 ± 3% at 0.1 μM), APV (5 ± 4%) and CBF (14 ± 6%), similar in magnitude to intracoronary nitroglycerin 10 μM. The vasodilator response was accentuated when the coronary vasculature was preconstricted with either endothelin-1 10 nM (increase in CBF: 27 ± 6%) or acetylcholine 10 nM. Pre-treatment with the nitric oxide synthase inhibitor nitro-L-arginine methylester (100 μM) did not inhibit BNP induced vasodilation in epicardial arteries, but significantly attenuated BNP-induced increase in CBF from 14 ± 6% to −3 ± 8%. In another group of pigs (n = 6), pre-treatment with the cyclooxygenase inhibitor indomethacin (2 mg/kg IV) induced transient elevations in blood pressure, and significantly attenuated BNP-induced increase in CSA from 10 ± 3% to −2 ± 3%. We conclude that BNP is a potent epicardial coronary vasodilator, especially in preconstricted arteries, with less effects on coronary resistance arteries. This effect may explain BNP-induced amelioration of coronary vasospasm. BNP-induced epicardial coronary vasodilation may partially be mediated via release of prostaglandins that have been suggested to influence cGMP in smooth muscle.

1052-149 The Effect of Sumatriptan on the Human Coronary Circulation

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Previous studies have shown that serotonin is released in the coronary circulation in patients with unstable angina and during PTCA. There are conflicting data regarding serotonin receptors in human coronary arteries. Both constriction and dilation of coronary arteries have been observed after stimulation of 5-hydroxytryptamine (5HT) receptors. This study examined the effect of a selective 5HT1 receptor agonist, sumatriptan, on the coronary circulation of 8 patients. Coronary artery diameter (Diameter) and blood flow (CBF) were measured after intracoronary acetylcholine (ACh), adenosine (ADO), and nitroglycerin (NTG), and after intravenous sumatriptan 0.1 mg/min × 30 min. Diameter was measured by computerized quantitative angiography. CBF was calculated from Diameter and coronary flow velocity measured with a Doppler guidewire.

	ACh	ADO	NTG	Sumatriptan
Diameter	+16 ± 4%	+32 ± 8%	+26 ± 12%	−7 ± 6%
CBF	+40 ± 21%	+378 ± 116%	+68 ± 37%	−17 ± 7%

X ± SEM expressed as percent change from baseline

Diameter increased after both ACh, an endothelium-dependent vasodilator, and NTG, an endothelium-independent vasodilator. CBF increased after ACh, ADO, and NTG. Neither Diameter nor CBF increased during sumatriptan infusion. Thus, intravenous sumatriptan did not dilate epicardial or resistance coronary arteries despite evidence of preserved endothelium-dependent and endothelium-independent vasodilation. The results suggest that 5HT1 receptors are not an important mechanism of coronary vasodilation in the human heart.

1052-150 Hypoxemia Stimulates Release of Endothelin I in Obstructive Sleep Apnoea Syndrome

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Endothelin I (ET I) and Angiotensin II (AT II) are strong known vasoconstric-